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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/927,161	08/10/2001	Maria R. Diaz-Torres	GC627-2	3999

5100 7590 07/27/2004

GENENCOR INTERNATIONAL, INC.  
ATTENTION: LEGAL DEPARTMENT  
925 PAGE MILL ROAD  
PALO ALTO, CA 94304

EXAMINER

SHIBUYA, MARK LANCE

ART UNIT	PAPER NUMBER
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1639

DATE MAILED: 07/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/927,161

Applicant(s)

DIAZ-TORRES ET AL.

Examiner

Mark L. Shibuya

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 4/19/2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,4-7 and 9-12 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,4-7 and 9-12 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.
- ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: \_\_\_\_\_.

**DETAILED ACTION**

***Status of the Claims***

1. Claims 1, 4-7, and 9-12 are pending. Claims 2, 3, 8, and 13-19 were canceled in the amendment to the claims, filed 4/19/2004. Claims 1, 4-7, and 9-12 are examined.

***Claim Rejections - 35 USC § 112, Second Paragraph***

***Withdrawn Claim Rejections***

2. The rejections of claims 1-12 under 35 U.S.C. 112, second paragraph, as set forth in the previous Office action, mailed 10/20/2003, are withdrawn in view of applicant's amendments to the claims, filed 4/19/2004.

***New Claim Rejections - 35 USC § 112, Second Paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1, 4-7, and 9-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by the amendments to the claims, filed 4/19/2004.

Claim 1 recites the term "non-heterologous sequences", which renders the claim vague and indefinite because the claim term is not defined by the claim, the specification does not provide a definition for the term, and one of skill in the art would not be reasonably apprised of the scope of the invention.

Claim 9 recites the limitation "said stuffer sequences flank said non-homologous sequences that flank said homology boxes" in lines 2-3. There are insufficient antecedent bases for the limitations "said stuffer sequences" and "said non-homologous sequences" in the claim.

***Claim Rejections - 35 USC § 112***

***Maintained Claim Rejections - 35 USC § 112, First Paragraph***

Claims 1, 4-7, and 9-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **Written Description Rejection**. This rejection maintains the grounds for rejection of claims 1-12 as set forth in the previous Office action, mailed 10/20/2003. The rejection is necessitated further by the amendments to the claims, filed 4/19/2004.

In the Reply, filed 4/19/2004, to the previous Office action, applicant argues that the amendments to claims provide the structure required and that the specification and claims describe the claimed methods of the present invention. Applicant argues that the amendments to the claims reciting that the microorganism is *Bacillus*, and that the DNA construct comprises an incoming sequence flanked by homology boxes, as well as further flanking non-homologous sequences which serve as non-critical targets for initiation of uptake of the DNA construct would reasonably convey to one skilled in the art that the applicant had possession of the claimed invention.

Applicant's arguments have been fully considered but they are deemed not persuasive. The specification does not provide representative examples of DNA constructs to convey possession of the claimed invention. The specification does not provide examples of incoming sequences of a variety of lengths, for example. The specification does not provide examples of varying degrees of homology for the homology boxes, or variations in the size of homology boxes. The specification does not provide varying examples of homology (or non-homology) of non-heterologous sequences flanking homology boxes, or variations in the size of the non-heterologous sequences flanking homology boxes. The specification does not provide variations in base pair distances between flanking non-heterologous sequences and the homology boxes they flank.

It may be noted that in the Reply filed 4/19/2004, applicant's arguments point to flanking "non-homologous regions" but that the claims, in fact, recite the term "non-heterologous sequences".

*New Claim Rejections - 35 USC § 112, First Paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 4-7, and 9-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a *New Matter Rejection*.

This rejection is necessitated by the amendments to the claims, filed 4/19/2004.

Claim 1 was amended in the amendments to the claims, filed 4/19/2004, to recite the limitation "said homology boxes are flanked by **non-heterologous** sequences which are non-critical targets". Amended claim 9 recites the language "stuffer sequences flank said non-homologous sequences that flank said homology boxes". Amended claim 12 recites the language "increasing the amount of sequence homology between said target sequence and at least one of said homology boxes". The examiner respectfully submits that there are no support for these limitations in the Specification as filed.

The applicant, in the Reply, filed 4/19/2004, to the previous Office action, mailed 10/20/2003, at p. 5, para 1, states that support for this limitation may be found, for example, at p. 7, line 13-p. 8, line 9; p. 9, lines 21-26; p. 12, lines 13-27; p. 4, lines 23-25 and Figure 2. These citations refer to non-homologous sequences. However, these citations do not disclose "non-heterologous" sequences, as recited in claim 1, and do not disclose "non-heterologous" sequences that flank homology boxes, and are non-critical targets for Bacilli to initiate uptake of the DNA constructs of the claimed invention. It is not disclosed by the specification that non-heterologous sequences can function as non-critical targets for Bacilli to initiate uptake of the DNA constructs of the claimed invention (but see, e.g., the instant Specification at p. 12, lines 13-27).

The Specification as filed does not disclose stuffer sequences that flank non-homologous sequences that flank said homology boxes, as in claim 9, but instead

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states at p. 8, lines 5-9, that stuffer sequences means any extra DNA that flanks the homology boxes, typically vector sequences, but could be any non-homologous DNA sequence. Thus amended claim 9 may be interpreted to encompass stuffer boxes that flank stuffer boxes that flank homology boxes; there is no literal support, in the Specification as filed, for such a limitation.

The Specification as filed does not disclose increasing the homology of a homology box, as in claim 12. The Specification, at p. 9, lines 21-26, states that the sequence of each homology box is homologous to a sequence in the *Bacillus* chromosome (i.e., homologous to the target sequence). The Specification does not disclose how to increase the homology of a homology box.

5. Claims 1, 4-7, and 9-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether undue experiment is necessitated. These factors can include, but are not limited to:

- (1) the breadth of the claims;
- (2) the nature of the invention;
- (3) the state of the prior art;
- (4) the relative skill of those in the art;

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- (5) the level of predictability in the art;
- (6) the amount of direction provided by the inventor;
- (7) the existence of working examples; and
- (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1 and 2) The breadth of the claims and the nature of the invention: The claims are drawn to methods of producing a transformed *Bacillus sp.* comprising producing a DNA construct in vitro, wherein said DNA construct comprises an incoming sequence of interest, flanked on each side by a homology box, wherein said homology boxes are flanked by **non-heterologous** sequences which are non-critical targets for said microorganism to initiate uptake of said DNA construct and transforming the *Bacillus* with the DNA construct such that the construct becomes integrated into the chromosome of the *Bacillus*.

However, there is insufficient guidance and direction as to how to make and use a DNA construct comprising an incoming sequence of interest, flanked on each side by a homology box, wherein said homology boxes are flanked by **non-heterologous** sequences which are non-critical targets for said microorganism to initiate uptake of said DNA construct. The specification does not disclose how one of skill in the art would distinguish between a homology box and non-heterologous, *i.e.*, homologous, sequences that flank the homology box. It is not disclosed where the homology boxes would end and the non-heterologous sequences would begin or whether non-heterologous sequences would provide a noncritical target for the cell to initiate DNA uptake.



(3 and 5) The state of the prior art and the level of predictability in the art. The prior art does not teach a DNA construct comprising an incoming sequence of interest, flanked on each side by a homology box, wherein said homology boxes are flanked by **non-heterologous** sequences which are non-critical targets for said microorganism to initiate uptake of said DNA construct. It is unpredictable, and probably logically impossible, that one of skill in the art could distinguish between homology boxes and homologous sequences that flank them.

(4) The level of one or ordinary skill: The level of skill would be high, most likely at the Ph.D. level. However, even such persons of ordinary skill in this art, given its probable logical impossibility, would be unable to make and use the invention as claimed.

(6-7) The amount of direction provided by the inventor and the existence of working examples: The Specification states:

Stuffer sequence means any extra DNA that flanks the homology boxes, typically vector sequences, but could be any **non-homologous** DNA sequence. Not to be limited by any theory, a stuffer sequence provides a noncritical target for a cell to initiate DNA uptake.

Specification at p. 8, lines 5-9. However the Specification does not disclose a DNA construct comprising an incoming sequence of interest, flanked on each side by a homology box, wherein said homology boxes are flanked by **non-heterologous** sequences which are non-critical targets for said microorganism to initiate uptake of said DNA construct and the specification does not provide any working examples of such.

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: The instant specification does not provide to one skilled in the art a reasonable amount of guidance with respect to the direction in which the experimentation should proceed in carrying out the full scope of the claimed methods. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 and n.23, 20 USPQ2d 1438, 1455 and n.23 (Fed. Cir. 1991). Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure, undue experimentation would be required of one of ordinary skill in the art to practice the full scope of the claimed invention.

### ***Claim Rejections - 35 USC § 102***

#### ***Withdrawn Claim Rejections***

6. The rejections of claims 1-12 under 35 U.S.C. 102(b), as anticipated by Hahn et al., *Molecular Microbiology* 21 (4): 763-775, 1996, as set forth in the previous Office action, mailed 10/20/2003, are withdrawn in view of applicant's amendments to the claims, filed 4/19/2004.

The reference of Hahn et al. does not teach DNA constructs comprising non-heterologous sequences flanking homology boxes.

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7. The rejections of claims 1-3, and 6-9 under 35 U.S.C. 102(b), as anticipated by Niaudet et al., Journal of Bacteriology 163 (1): 111-120, 1985, as set forth in the previous Office action, mailed 10/20/2003, are withdrawn in view of applicant's amendments to the claims, filed 4/19/2004.

The reference of Niaudet et al. does not teach DNA constructs comprising non-heterologous sequences flanking homology boxes.

8. The rejections of claims 1-4, 5-7, 10 and 11 under 35 U.S.C. 102(b), as anticipated by van Sinderen and Venema, Journal of Bacteriology 176 (18): 5762-5570, 1994, as set forth in the previous Office action, mailed 10/20/2003, are withdrawn in view of applicant's amendments to the claims, filed 4/19/2004.

The reference of van Sinderen and Venema et al. does not teach DNA constructs comprising non-heterologous sequences flanking homology boxes.

9. The rejections of claims 1-3, 6, 7, 10, and 11 under 35 U.S.C. 102(b), as anticipated by Fahnestock et al., EPO 761815A2, as set forth in the previous Office action, mailed 10/20/2003, are withdrawn in view of applicant's amendments to the claims, filed 4/19/2004.

The reference of Fahnestock et al. does not teach DNA constructs comprising non-heterologous sequences flanking homology boxes.

10. The rejections of claims 1-3, 6 and 7, 10, and 11 under 35 U.S.C. 102(b), as anticipated by Fahnstock et al., US 4,828,994, as set forth in the previous Office action, mailed 10/20/2003, are withdrawn in view of applicant's arguments and amendments to the claims, filed 4/19/2004.

The reference of Fahnstock et al. does not teach DNA constructs comprising non-heterologous sequences flanking homology boxes.

### ***Conclusion***

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. All claims stand finally rejected.

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13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Shibuya whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
PADMASHRI PONNALURI  
PRIMARY EXAMINER

Mark L. Shibuya  
Examiner  
Art Unit 1639

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